Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for sequencing a terminal portion of an oligomer, comprising:

(a) contacting said oligomer with a mass defect labeling moiety to covalently attach ~~a~~ **the mass defect labeling moiety** ~~label~~ to ~~the~~ **a** terminus of the oligomer and form a labeled oligomer, said **mass defect** labeling moiety comprising at least one element having an atomic number from 17 to 77, with the proviso that said element is other than sulfur or phosphorus;

(b) fragmenting said labeled oligomer using an enzymatic, chemolytic or mass spectrometric fragmentation method to produce labeled oligomer fragments; ~~and~~

(c) **identifying a mass spectrum data corresponding to said labeled oligomer fragments; and**

(d) determining the sequence of at least two terminal residues of said labeled oligomer, **wherein** said sequence determination step ~~comprising identifying a mass spectrum data corresponding to said labeled oligomer fragment or a mass spectrum fragment thereof, wherein said identification step~~ is based at least in part on the mass defect ~~of at least a portion~~ of said labeling moiety.

2. (Original) The method of claim 1, wherein said labeling moiety comprises at least one element of atomic number 35 to 63.

3. (Original) The method of claim 2, wherein said labeling moiety comprises at least one element of atomic number 39 to 58.

4. (Original) The method of claim 2, wherein said labeling moiety comprises at least one element selected from the group consisting of bromine, iodine, europium and yttrium.

5. (Original) The method of claim 4, wherein said element is europium.

6. (Original) The method of claim 4, wherein said element is yttrium.

7. (Original) The method of claim 4, wherein said element is bromine.

8. (Original) The method of claim 4, wherein said element is iodine.

9. (Original) The method of claim 1, wherein said oligomer is selected from the group consisting of a protein, an oligonucleotide, an oligosaccharide and a lipid.

10. (Original) The method of claim 9, wherein said oligomer is an oligonucleotide.

11. (Original) The method of claim 9, wherein said sequence is at least three residues.

12. (Original) The method of claim 9, wherein said sequence is at least four residues.

13. (Original) The method of claim 1, wherein several oligomers, each labeled with a different number of mass defect elements are mixed prior to said fragmenting or analyzing step.

14. (Currently Amended) A method for sequencing a portion of an oligomer in an oligomer mixture, said method comprising:

(a) contacting said oligomer mixture with a terminus labeling moiety to covalently attach ~~a~~ **the terminus labeling moiety** ~~label~~ to ~~the~~ **a** terminus of said oligomer and form a labeled oligomer mixture, said terminus labeling moiety comprising at least one element

having an atomic number from 17 to 77, with the proviso that said element is other than sulfur or phosphorus;

(b) separating individual labeled oligomers in said labeled oligomer mixture; ~~and~~

(c) **identifying a mass spectrum data corresponding to said individual labeled oligomer; and**

(d) analyzing said **mass spectrum data** ~~individual labeled oligomers from step (b) by a mass spectrometric method~~ to determine the sequence of at least two terminus residues **of said oligomer**, **wherein** said analysis step ~~comprising identifying a mass spectrum data corresponding to said labeled oligomer or a mass spectrum fragment thereof, wherein said identification step~~ is based at least in part on the mass defect ~~of at least a portion~~ of said labeling moiety.

15. (Original) A method in accordance with claim 14, wherein said element has an atomic number of from 35 to 63.

16. (Original) A method in accordance with claim 14, wherein said element has an atomic number of from 39 to 58.

17. (Original) A method in accordance with claim 14, wherein said element is selected from the group consisting of bromine, iodine, europium and yttrium.

18. (Original) A method in accordance with claim 14, further comprising a step prior to step (a) of isolating a group of oligomers from a biological sample.

19. (Original) A method in accordance with claim 18, wherein said biological sample is from a diseased tissue sample.

20. (Original) A method in accordance with claim 18, wherein said biological sample is from a healthy tissue sample.

21. (Original) A method in accordance with claim 14, wherein said separating is conducted by at least one method of capillary electrophoresis of the labeled oligomer mixture.

22. (Original) A method in accordance with claim 14, wherein said mass spectrometric method uses ESI-TOF MS.

23. (Currently Amended) A method for structure and function analysis of an oligomer having a plurality of residues, said method comprising:

(a) contacting said oligomer with a mass defect labeling reagent to differentially label exposed residues and unexposed residues and produce a differentially labeled oligomer comprising a mass defect labeling moiety, wherein said mass defect labeling reagent comprises at least one element having an atomic number of from 17 to 77 that is other than sulfur or phosphorus;

(b) **identifying a mass spectrum data corresponding to said differentially labeled oligomer; and**

(c) analyzing said **mass spectrum data** ~~differentially labeled oligomer by a mass spectrometric method~~ to determine sequences of said oligomer that are exposed in the three-dimensional structure and sequences of said oligomer that are unexposed in the three-dimensional structure, **wherein** said analysis step ~~comprising identifying a mass spectrum data corresponding to said labeled oligomer or a mass spectrum fragment thereof, wherein said identification step~~ is based at least in part on the mass defect of ~~at least a portion of~~ said labeling moiety.

24. (Original) A method in accordance with claim 23, wherein said oligomer is a protein, a nucleic acid, or an oligosaccharide.

25. (Original) A method in accordance with claim 23, wherein said mass defect labeling reagent comprises at least one element of atomic number 35 to 63.

26. (Original) A method in accordance with claim 26, wherein said mass defect labeling reagent is bromine and said oligomer is a protein.

27. (Original) A method in accordance with claim 23, wherein said mass defect labeling reagent comprises at least one element of atomic number 39 to 58.

28. (Original) A method in accordance with claim 23, wherein said differentially labeled oligomer is fragmented by enzymatic or chemolytic methods prior to step (b).

29. (Original) A method in accordance with claim 23, wherein said oligomer is a protein, said mass defect is bromine or iodine and said exposed residues comprises a portion of the tyrosine residues present in said protein.

30. (Original) A method in accordance with claim 23, wherein said mass spectrometric method uses ESI-TOF MS.

31. (Original) A method in accordance with claim 29, wherein said mass spectrometric method uses ESI-TOF MS.

32. (Currently Amended) A method for sequencing the terminal portion of an oligomer, comprising:

(a) contacting a first sample of said oligomer with a labeling moiety to covalently attach a label to the terminus of the oligomer and form a labeled oligomer, said labeling moiety having one element with an atomic number from 17 to 77, with the proviso that said element is other than sulfur or phosphorus;

(b) contacting a second sample of said oligomer with a labeling moiety to covalently attach a label to ~~the~~ a terminus of the oligomer and form a labeled oligomer, said labeling moiety having two elements with an atomic number from 17 to 77, with the proviso that said elements are other than sulfur or phosphorus;

(c) optionally, repeating step (b) from one to three times with additional samples, wherein the labeling moieties have three, four or five elements, respectively, with an atomic number from 17 to 77, with the proviso that said elements are other than sulfur or phsophorus;

(d) mixing the labeled oligomers from steps (a) through (c);

(e) fragmenting said labeled oligomers using an enzymatic, chemolytic or mass spectrometric fragmentation method to produce labeled oligomer fragments; ~~and~~

(f) **identifying a mass spectrum data corresponding to said labeled oligomer fragments; and**

(g) determining the sequence of at least two terminal residues of said labeled oligomer fragments, **wherein** said sequence determination step ~~comprising identifying a mass spectrum data corresponding to said labeled oligomer fragment or a mass spectrum fragment thereof, wherein said identification step~~ is based at least in part on the mass defect of ~~at least a portion of~~ said labeling moiety.

33. (Original) The method of claim 32, wherein each of said elements has an atomic number of from 35 to 63.

34. (Original) The method of claim 32, wherein each of said elements has an atomic number of from 39 to 58.

35. (Original) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is a protein.

36. (Original) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is an oligonucleotide.

37. (Original) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is an oligosaccharide.

38. (Currently Amended) A method for sequencing a portion of an oligomer, comprising:

(a) fragmenting aliquots of said oligomer using one or more specific enzymatic or chemolytic fragmentation methods to produce oligomer fragments, wherein a different fragmentation method is applied to each aliquot;

(b) contacting a first aliquot of oligomer fragments with a first labeling moiety to covalently attach said first labeling moiety to ~~the~~ **a** terminus of the oligomer fragments and form labeled oligomer fragments, said first labeling moiety having one element with an atomic number from 17 to 77, with the proviso that said element is other than sulfur or phosphorus;

(c) optionally contacting the other aliquots of oligomer fragments with other distinct labeling moieties to covalently attach said distinct labeling moieties to the termini of the oligomer fragments and form labeled oligomer fragments, said distinct labeling moiety having two or more elements with an atomic number from 17 to 77, with the proviso that said elements are other than sulfur or phosphorus;

(d) optionally mixing the aliquots of labeled oligomer fragments; ~~and~~

(e) **identifying a mass spectrum data corresponding to said labeled oligomer fragments; and**

(f) determining the sequence of at least two residues of said labeled oligomer, **wherein** said sequence determining step ~~comprising identifying a mass spectrum data corresponding to said labeled oligomer or a mass spectrum fragment thereof, wherein said identification step~~ is based at least in part on the mass defect ~~of at least a portion~~ of said labeling moiety.

39. (Original) A method in accordance with claim 38, wherein said oligomer is a lipid.

40. (Original) A method in accordance with claim 38, wherein said oligomer is a protein.

41. (Original) A method in accordance with claim 38, wherein said oligomer is a nucleic acid.

42. (Original) A method in accordance with claim 38, wherein said oligomer is an oligosaccharide.

43. (Original) A method in accordance with claim 38, wherein said elements have an atomic number of from 35 to 63.

44. (Original) A method in accordance with claim 43, wherein said elements have an atomic number of from 39 to 58.

45. (Currently Amended) A method for comparing the relative abundances of analytes from two or more samples, comprising:

(a) contacting the analytes of the first sample with a labeling moiety to covalently attach a label to the analytes and form labeled analytes, said labeling moiety having one element with an atomic number from 17 to 77, with the proviso that said element is other than sulfur or phosphorus;

(b) contacting the analytes of subsequent samples with labeling moieties to covalently attach labels to the analytes in each sample, wherein the labeling moieties used for each subsequent sample contain an additional element with an atomic number from 17 to 77, with the proviso that said elements are other than sulfur or phosphorus;

(c) mixing the aliquots of labeled analytes; ~~and~~

(d) **identifying mass spectrum data corresponding to said labeled analytes; and**

(e) analyzing said **mass spectrum data** ~~labeled analytes using a mass spectrometric fragmentation method~~ to determine the relative abundances of one or more of the analytes between the samples, **wherein** said analysis step ~~comprising identifying mass spectrum~~

~~data corresponding to said labeled analytes or a mass spectrum fragment thereof, wherein said identification step~~ is based at least in part on the mass defect of ~~at least a portion of~~ said labeling moiety.

46. (Original) A method in accordance with claim 45, wherein said elements have an atomic number of from 35 to 63.

47. (Original) A method in accordance with claim 45, wherein said elements have an atomic number of from 39 to 58.

48. (Currently Amended) A method for tagging the elements of chemical libraries, either during synthesis or screening, comprising;

(a) contacting a root tag with a labeling moiety to covalently attach a label to the root tag and form a labeled tag, said labeling moiety having one element with an atomic number from 17 to 77, with the proviso that said element is other than sulfur or phosphorus;

(b) optionally, contacting a root with additional labeling moieties to covalently attach additional labels to the root tag and form a multiply labeled tag, said labeling moiety having one element with an atomic number from 17 to 77, with the proviso that said element is other than sulfur or phosphorus; ~~and~~

(c) **identifying mass spectrum data corresponding to said labeled tag; and**

(d) analyzing the **mass spectrum data** ~~labeled tag by mass spectrometric methods~~ to determine both ~~its~~ **the** mass and the number of elements with an atomic number from 17 to 77 **of the labeled tag**, such that the mass and number of elements identifies ~~the~~ chemical processes to which ~~the~~ **a** specific chemical of the library has been exposed and the identity of the chemical from the library, **wherein** said analysis step ~~comprising identifying mass spectrum data corresponding to said labeled tag or a mass spectrum fragment thereof, wherein said identification step~~ is based at least in part on the mass defect ~~of at least a portion~~ of said labeling moiety.

49. (Original) A method in accordance with claim 48, wherein said elements have an atomic number of from 35 to 63.

50. (Original) A method in accordance with claim 48, wherein said elements have an atomic number of from 39 to 58.

51. (Previously presented) The method of claim 1, wherein said sequence determination step comprises identifying a mass spectrum peak of a fragment comprising said labeling moiety based on the mass defect of said labeling moiety.

52. (Previously presented) The method of claim 45, wherein at least a portion of said labeling moiety of step (a) is a stable isotope of said labeling moiety of step (b).

53. (Previously presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 2 or more but 16 or less stable isotopes.

54. (Previously presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 4 or more but 16 or less stable isotopes.

55. (Previously presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 8 or more but 16 or less stable isotopes.

56. (Previously presented) The method of claim 52, wherein said stable isotope is selected from the group consisting of ^{2}H, ^{13}C, ^{15}N and ^{81}Br.

57. (Previously presented) The method of claim 45, further comprising separating at least a portion of said mixture of labeled analytes prior to said analysis step (d).

58. (Previously presented) The method of claim 57, wherein said separation step comprises separating at least a portion of said mixture of labeled analytes by electrophoresis, chromatography or affinity separation.

REMARKS

A. Status of the Claims and Support for Amendments

Claims 1-58 are pending. Claims 1, 14, 23, 32, 38, 45, and 48 are currently amended.

Claims 1, 14, 23, 32, 38, 45, and 48 have been amended to emphasize that the methods of the claimed inventions include a separate step of identifying a mass spectrum data corresponding to labeled oligomer fragments, individual labeled oligomers, differentially labeled oligomers, labeled analytes, or labeled tags.

Support for the amendments to claims 1, 14, 23, 32, 38, 45, and 48 can be found in the claims as originally filed and throughout the specification and, for example, at page 20, lines 19-27 (stating, in part, "[p]referred labels impart a unique mass signature to ***the fragments to which they are attached,***" emphasis added); at page 23, lines 22-25 ("[i]n contrast, the present invention provides that labeling is carried out using *only* labels having a mass defect, to distinguish the labeled fragments from unlabeled fragment and provide a more robust, yet sensitive method"); at page 32, lines 14-29 (stating, in part, "it is possible to easily distinguish the signal peaks from labeled fragments that lie off this periodic spacing, such as labeled fragments wherein the label contains one or more elements with an unusual nuclear binding energy"); and at page 33, lines 20-34 (stating, in part "abundant isotope pairs will only exist for labeled fragments in the mass spectrum and the isotopes typically exhibit similar ionization and fragmentation efficiencies").

Therefore, no new matter has been added with this amendment.

B. Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 7-15, 17-25, 28, 30-33, 36-38, 41-43, 45-46, 48-49, and 51-58 stand rejected under 35 U.S.C. 103(a) as obvious over Brennan, U.S. Patent No. 5,174,962 (hereinafter referred to as "Brennan") in view of Schmidt *et al.*, U.S. Patent No. 56,287,780 B1 (hereinafter referred to as "Schmidt"). Claims 3, 5, 6, 16, 27, 34, 44, 47, and 50 stand rejected under 35 U.S.C. 103(a) as obvious over Brennan in view of Schmidt, further in view of Meyer *et*

al., U.S. Patent No. 6, 359, 111 B1 (hereinafter referred to as "Meyer"). Claims 26, 29, 35, 39, and 40 stand rejected under 35 U.S.C. 103(a) as obvious over Brennan, in view of Schmidt, further in view of Chait *et al.*, U.S. Patent No. 6, 391, 649 B1 (hereinafter referred to as "Chait").

The Examiner asserts that it would have been obvious to use the fluorinated mass label of Schmidt in the methods of Brennan to achieve Applicants' invention as recited in claims 1, 14, 23, 32, 38, 45 and 48.

As discussed in detail below, Applicants respectfully traverse because:

1. The fluorinated mass labels of Schmidt are ***cleaved*** and then detected using mass spectrometry, whereas Applicants' mass defect label is detected while it is ***attached*** to the respective oligomer, oligomer fragment, analyte, or tag.

2. One of skill in the art would recognize that it would be undesirable to use the fluorinated mass label of Schmidt in the sequencing methods of Brennan.

1. *Burden of Procedure in Establishing Prima Facie Obviousness*

"The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal arguments or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988)." *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The Federal Circuit has held that "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382 (CCPA 1970). In addition, the mere fact that references can be combined or modified does not render the

resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F. 2d 680 (Fed. Cir. 1990); MPEP § 2143.02.

As explained below, Applicants submit that the cited references do not teach all the claimed elements and fail to provide a suggestion or motivation to make the proposed combination.

2. ***The combination of Brennan and Schmidt fails to teach or suggest each element in claims 1, 14, 23, 32, 38, 45 and 48, as amended***

In the method practiced by Schmidt, the fluorinated mass labels are ***cleaved*** prior to detection by mass spectrometry. For example, at column 5, lines 34-38, Schmidt states:

> An advantageous embodiment of this invention ***where cleavable mass labels are employed*** is the use of fluorinated mass labels when high-resolution mass analysis of labels is employed ***after cleavage of mass labels from their nucleic acid.***

From this passage, it is clear that the fluorinated mass labels of Schmidt are identified by mass spectrometry only after cleavage from their nucleic acid. Thus, Schmidt teaches a technique for detecting the presence of a nucleic acid by identifying a detached fluorinated mass label using mass spectrometry. There is no teaching or suggestion in Schmidt to detect a mass defect label while it is attached to an oligomer, analyte, or tag.

In contrast, Applicants' mass defect label is detected while it is ***attached*** to the respective oligomer, oligomer fragment, analyte, or tag. Claims 1, 14, 23, 32, 38, 45 and 48 now recite "***identifying*** a mass spectrum data corresponding to ***labeled*** oligomers," "***labeled*** oligomer fragments," "individual ***labeled*** oligomers," "differentially ***labeled*** oligomers," "***labeled*** analytes," and "***labeled*** tags." In addition to emphasizing that the oligomers, analytes, and tags are labeled when detected by mass spectrometry, the claims now specify that the mass spectrum data analysis or sequence determination "is based at least in part on the mass defect of said labeling moiety."

There is no teaching or suggestion in Brennan, Meyers, or Chait that would remedy the deficiency in Schmidt. Brennan, Meyers and Chait all fail to disclose mass defect

labels altogether, much less a mass defect label that is attached to an oligomer, oligomer fragment, analyte, or tag.

Therefore, because the cited references do not teach or suggest identifying a mass defect label that is ***attached*** to an oligomer, oligomer fragment, analyte, or tag, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

3. ***The cited references do not suggest the desirability of using the fluorinated mass label of Schmidt in the sequencing methods of Brennan***

Brennan teaches methods useful in "sequencing natural or recombinant DNA and other polynucleotides" (see abstract). Brennan does not teach or suggest the use of mass defect labels at all, much less a shortcoming in the disclosed sequencing methods that could be remedied by the use of a fluorinated mass label.

Schmidt discloses fluorinated mass labels useful as "mass markers for labeling nucleic acids and other molecules" (see column 1, lines 5-6). ***Schmidt does not teach or suggest sequencing oligomers*** using the disclosed "mass markers," much less sequencing with fluorinated mass labels.

In fact, Applicants respectfully submit that substituting the isotopic labels of Brennan with the fluorinated mass labels of Schmidt would be ***un***desirable. In Applicants' written description, the "limited utility" of Schmidt's fluorine mass defect markers is discussed in detail (see page 21, lines 13-27 stating, in part, "[i]n contrast to the limited utility of F as a mass defect element (Schmidt et al. WO 99/32501 (July 1, 1999)) the present invention uses mass defect elements that present a much greater mass difference and thus broader utility"; see also page 5, line 8, to page 6, line 17). Applicants' disclosure is evidence that the fluorinated mass labels of Schmidt are generally undesirable. Thus, after examining Brennan and Schmidt, one skilled in the art would not be motivated to substitute the isotopic labels of Brennan with the fluorinated mass labels of Schmidt, which Applicants have disclosed as having limited utility.

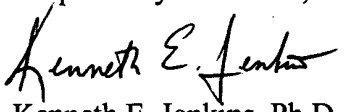
Because one skilled in the art would recognize the limited utility of Schmidt's fluorine mass defect markers, there would be no motivation to combine Schmidt and Brennan. Therefore, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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